VITAMIN D
UpDates

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EDITORIAL

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Dear Readers,

In this issue, we feature an update by Prof. Peroni on the role of vitamin D in pediatric patients as well as one by Prof. Triggiani on the effects of vitamin D in the prevention of cerebrovascular diseases.
Just think: only two years have passed since their previous contributions, and already we need updates!
In a balanced and objective manner, both authors admit that even though vitamin D has recognized biological effects, which go far beyond benefits to the skeletal system, studies that propose to assess the impact on the prevention or improvement of pathologies that are attributed to vitamin D deficiency are often contradictory, at least at present. Indeed, the results of clinical trials that are currently available have generally failed to show significant improvement in endpoints for the extra-skeletal system, for benefits in pediatric patients and for cerebrovascular diseases.
Nonetheless, both authors agree that this contradiction – between preclinical observations and associated observational studies, on the one hand, and the results of conducted trials, on the other – rather than casting doubt creates the premises for further research on the role of vitamin D in the prevention of extra-skeletal outcomes. They conclude that it is necessary to acquire new data to better assess optimal doses, the duration of supplementation, and optimal serum levels to attain positive biological and clinical results. In fact, current analysis of outcome data from the trials does not allow us to exclude the possible beneficial effect of vitamin D in extra-skeletal contexts. It is indeed possible to identify a fourfold order of factors responsible for negative results, as summarized in a recent publication of the Verona school [1]: a study population which did not show high risk for the evaluated event, the presence of co-factors that were not adequately assessed, a period of observation insufficiently long to evaluate the outcome, and pre-supplementation vitamin D levels that were not deficient, an essential requirement if we believe that vitamin D acts as a nutrient, in other words that it is useful only when it is missing.

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In addition, as was recently hypothesized by French colleagues, another intriguing explanation is also possible, namely the "autacoid paradigm". The term "autacoid" derives from the Greek *autos* (self) and *akos* (remedy). This system posits that molecules are produced and act locally, "upon request" at the intercellular or tissue level by means of autocrine or paracrine signaling.

As you know, at the level of circulation the endocrine system effectively aims to guarantee constant levels of $1,25(OH)_2D$ by means of refined regulation, in spite of the great variability of 25(OH)D levels due to the degree of exposure to sun or intake through food or supplementation, with the exception of conditions of great deficiency or extreme vitamin D overload. Nonetheless, an important form of vitamin D metabolism – by both the extra-hepatic 25-hydroxylase and the extra-renal 1α-hydroxylase enzymes – has been recently discovered, such as that at the skin and the adipose tissue levels and of the immune and nervous systems. In these various tissues, expression of these enzymatic activities and of vitamin D receptors indeed represent the "autacoid system". Contrary to the endocrine system, the autacoid system is inducible, as for example following inflammatory stimuli; it requires that local increase of $1,25(OH)_2D$ is transitory and self-limiting, thanks to the induction of deactivating 24-hydroxylase. The immunomodulatory functions of $1,25(OH)_2D$ are therefore temporally and spatially limited to the sources of inflammation and do not interfere with circulating serum levels of $1,25(OH)_2D$. It is clear that local synthesis of $1,25(OH)_2D$ requires that its precursors – 25(OH)D and especially cholecalciferol – are locally bioavailable: this depends both on their circulating levels and their tissue stocks.

This new paradigm – which is, then, quite different from what occurs in the endocrine system – in particular requires that the extra-skeletal effects of vitamin D also depend on the tissue reserves of vitamin D metabolites which are locally produced or inactivated. Given this paradigm, it should be clear that obtaining circulating levels of 25(OH)D in the systemic circulation is necessary but not sufficient, if at the tissue level adequate concentrations of active vitamin D metabolites are not obtained for some reason (insufficient induction? excessive catabolism? lack of cholecalciferol or of precursor metabolites?)

And yet, in present trials we evaluate only (and not even all the time!) circulating levels of 25(OH)D though not those of $1,25(OH)_2D$, let alone tissue concentrations, which are the functional ones, especially for extra-skeletal effects. You'll appreciate that this new paradigm, discovered a century after the endocrine system, opens the way to new and intriguing lines of research, such as the possibility that local administration of cholecalciferol or 25(OH)D may at times turn out to be a better option than oral supplementation in obtaining some extra-skeletal benefits. Might, for example, transcutaneous application of vitamin D at the breast level be more efficient than oral intake in preventing and treating breast cancer? Or might we even come to discourage covering the breasts to favor local cutaneous production of cholecalciferol?

What do you think?

I hope you enjoy reading this issue.

References

1. Gatti D, Bertoldo F, Adami G, et al. Vitamin D supplementation: much ado about nothing. Gyn Endocrinol 2020;36:185-9. https://doi.org/10.1080/09513590.2020.1731452
2. Chabrol T, Wion D. Randomized clinical trials of oral vitamin D supplementation in need of a paradigm change: the vitamin D autacoid paradigm. Med Hypotheses 2020;134:109417. https://doi.org/10.1016/j.mehy.2019.109417